REMARKS

The applicants thank the examiners for consideration of applicant's response filed on March 23, 2006. In order to advance prosecution, Applicants have amended claim 18 and dependent claims 19, 20 and 33-38 and have canceled claims 28-32.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

1. Priority

The Office Action asserts that the present invention is not entitled to priority to U.S. Provisional Patent Application No. 60/358,580, filed on 2/20/2002 because "[t]he priority provisional filed on 2/20/2002 expires within one year. There are no documents that arose from 60/358,580 for which priority is being claimed that recite the instantly claimed limitations above. The intervening references do not recite each of the instant limitations and therefore the instant application does not receive benefit of 60/358,580. PCT/US03/05346 did not arise from 60/358,580, and therefore does not receive benefit of this document" (See Office Action at page 3).

The Applicants respectfully traverse. As detailed in the previous response, dated March 23, 2006, the present application claims priority to, *inter alia*, U.S. Provisional patent application 60/358,580, filed February 20, 2002. The claims presented above all find support in this application, inter alia, at pages 4, 10, 11, 34, and 35. The present application claims priority to 60/358,580 through PCT/US03/05346, filed on 2/20/2003, which was filed within one year of 60/358,580 and which claims the benefit of 60/358,580. Furthermore, PCT/US03/05346 expressly incorporated 60/358,580 by reference in its entirety: ("This invention claims the benefit of Beigelman USSN 60/358,580 filed February 20, 2002 ... These applications are hereby incorporated by reference herein in their entireties, including the drawings" (see page 1

and cover page of WO 03/070918)). The presently claimed invention is fully supported by PCT/US03/05346, see for example pages 6, 10, 22, and 80-81 (reciting all of the instantly claimed cap moieties). Therefore, because the present invention properly claims the benefit of PCT/US03/05346, which properly claims the benefit of 60/358,580 and incorporated it by reference, and because both PCT/US03/05346 and 60/358,580 disclose all of the limitations of the presently claimed invention, the present invention is entitled to a priority date of February 20, 2002.

2. Claim Rejections under 35 U.S.C. § 112

Claims 19-38 are rejected under 35 U.S.C. 112, first paragraph, allegedly because "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims" with reference to the term "pharmaceutical composition". The Office action asserts that amendment of the claims to read "A composition comprising the double stranded nucleic acid molecule of claim 18 in a pharmaceutically acceptable carrier or diluent" would obviate the rejection. Claim 38 has been amended accordingly. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

3. Claim rejections under 35 U.S.C. § 103(a)

Claims 18-20, 28, 29, 33, 34, 37, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Bellon et al. (Nucleic Acids Research, 1993, Vol. 21, No. 7, pages 6877-6888) and Hammond et al. (Nature, 2001, Vol. 2, pages 110-119). Claims 28 and 29 have been canceled, thus rendering the rejection moot as applied to these claims. For the following reasons, the applicants respectfully traverse the rejection as it applies to the presently claimed invention.

The Applicants submit that the Office Action has still not established a *prima facie* case of obviousness with respect to the presently amended claims. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must

teach or suggest all the claim limitations. *See* MPEP §2143.

The Office Action combines the teachings of Elbashir and Bellon and asserts that "[i]t would be obvious to one of ordinary skill in the art to design a siRNA, as taught by Elbashir et al., wherein both of the strands include 4'-thio terminal cap moieties, as 4'-thio modifications are taught by Bellon et al." (see Office Action, page 9). The Office Action also asserts that because "Elbashir et al. teach…successful terminal modification of siRNA duplexes" that "one would have been motivated to incorporate a specific modification at these terminal locations, such as a 4'-thio modification that was known in the art…" (see Office Action at page 9). The Office Action then combines the teachings of Elbashir and Bellon with Hammond and asserts that "Hammond et al. teach that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression, thereby offering motivation to utilize dsRNA to inhibit target gene expression rather than a single stranded oligo, as taught by Bellon." (see Office Action, page 9).

In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the claimed invention. As acknowledged by the Examiner, "Elbashir teaches successful target inhibition with siRNA duplexes modified at 8 out of 42 nucleotides and teach that complete substitution of the duplex abolishes activity." (see Office Action, page 8) In fact, Elbashir was only able to modify the 3'-ends of siRNA duplexes with up to four 2'-deoxy nucleotides. In cases where there was complete substitution, either with 2'-deoxy or 2'-O-methyl modifications, RNAi activity was abolished. Elbashir expressly teaches that "2'-deoxy substitutions at the 2 nt 3'-overhanging ribonucleotides do not affect RNAi" but that "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly". (see Elbashir, page 6885) Importantly, in all cases where modifications existed at the 5'-position of either strand of the duplex, RNAi activity was abolished. Therefore, one of skill in the art would not have been motivated, nor would have any expectation of success, in modifying a duplex to include the *specific terminal cap modifications* as are presently claimed, *at both the 3' and 5'-ends of a first strand of a duplex, and the 3'-end of a second strand of a duplex*, as is presently claimed (*emphasis added*).

The Office relies on Caplen for its teachings that "[m]any of the problems associated with

developing RNAi as an effective therapeutic are the same as encounter with previous gene therapy approaches. The key issues of delivering nucleic acids to the require tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…" and concludes that it motivates incorporation of a 4′-thio modification as taught by the Bellon oligonucleotide art.

The applicants respectfully submit, however, that the Office has both misconstrued and misapplied Caplen's teachings. First, Caplen concludes that RNAi and prior gene therapy approaches have the ***same problems*** for the development as therapeutics; Caplen ***does not*** teach or suggest that RNAi and prior gene therapy approaches would have the ***same solutions***, as inherently presumed in the rejection. To render the claimed invention obvious, the prior art must teach or suggest the claimed solution. It does not.

Furthermore, the Office ignores Caplen's proviso, "***while ensuring an appropriate level of efficacy***…." Caplen recognized the obvious, ***i.e.***, that there would be no point in stabilizing a therapeutic molecule if its efficacy is eliminated. And the prior art provides insufficient teachings to provide the ordinary artisan with a reasonable expectation that modifying siRNA molecules in a manner as presently claimed would yield an active molecule. No prior art provided any insight as to how siRNA modifications affect the molecule's interaction with the RISC complex and the concomitant induction of target cleavage. Elbashir provided only a very small handful of examples with mixed results, some modified siRNA molecules retained RNAi activity while others did not. But neither Elbashir (nor any of the other art) provided any general teachings from which the ordinary artisan could derive an understanding as to the affect of siRNA modifications on the molecule's efficacy at inducing RNAi, nor did any of the art provide any specific teachings regarding how the instantly claimed modifications would affect the molecule's efficacy at inducing RNAi. In brief, the prior art provides insufficient teaching to imbue the ordinary artisan with a reasonable degree of assurance that modifying a double stranded RNA molecule as presently claimed would yield an active molecule. For this reason, too, the present claims cannot be obvious.

Nevertheless, in the interest of expediting prosecution, Claim 18 has been amended to remove the term "4'-thio nucleotide". As such, none of the cited references, when combined, teach or suggest all the claim limitations, thus obviating the rejection as applied to the present

claims. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of the 103(a) rejection as applied to instant claims 18-20, 33, 34, 37, and 38.

Claims 18-20, and 28-38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Bellon et al. (Nucleic Acids Research, 1993, Vol. 21, No. 7, pages 6877-6888); Hammond et al. (Nature, 2001, Vol. 2, pages 110-119); further in view of Parrish et al., (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, No. 4, pages 573-581). Claims 28-32 have been canceled, thus rendering the rejection moot as applied to these claims. For the following reasons, the applicants respectfully traverse the rejection as it applies to the presently claimed invention.

Contrary to the Office action's assertions, Parrish do not teach chemically synthesized double stranded siRNA molecules comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides. Instead, Parrish teach enzymatically synthesized long double stranded nucleic acid molecules having some 2'-deoxy-2'-fluoro substitutions. Nevertheless, Parrish does not remedy the defects of Elbashir, Bellon, and Hammond as described above with reference to the presently claimed invention because Parrish, alone or in combination with the other references, does not teach or suggest a duplex of the length presently claimed that includes the *specific terminal cap modifications* as presently claimed *at both the 3' and 5'-ends of a first strand of a duplex, and the 3'-end of a second strand of a duplex* as is presently claimed. Therefore, the combination of Elbashir, Bellon, Hammond and Parrish cannot render the present invention obvious.

Schmidt et al. teach hairpin ribozymes that can be linked with nucleotide or non-nucleotide linkers. Nevertheless, Schmidt does not remedy the defects of Elbashir, Bellon, Hammond, or Parrish as described above with reference to the presently claimed invention because Schmidt, alone or in combination with the other references, does not teach or suggest a duplex of the length presently claimed that includes the *specific terminal cap modifications* as presently claimed *at both the 3' and 5'-ends of a first strand of a duplex, and the 3'-end of a second strand of a duplex* as presently claimed. Therefore, the combination of Elbashir, Bellon, Hammond, Parrish, and Schmidt cannot render the present invention obvious. In view of all the foregoing, the applicants respectfully request reconsideration and withdrawal of the 103(a) rejection as

applied to instant claims 18-20, and 33-38.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone:312-913-0001
Facsimile: 312-913-0002